Dementia Precox Studies.

ADRENALIN: A NEW DIAGNOSTIC TEST FOR DEMENTIA PRECOX.

By Bayard Holmes, M. D.

Chicago.

Reprint from
THE ALIENIST AND NEUROLOGIST,
Vol. 36, No. 4, November, 1915
3858 West Pine Boulevard,
St. Louis

Digitized by the Internet Archive
in 2015

https://archive.org/details/dementiapraecoxs00holm

Dementia Precox Studies.

ADRENALIN: A NEW DIAGNOSTIC TEST FOR DEMENTIA PRECOX.

By Bayard Holmes, M. D.,

Chicago.

ANYTHING that will assist in an early diagnosis of dementia precox is a welcome scientific fact, and will receive wide appreciation, for the frequency of this disease seems to be increasing in the records of admissions to our state institutions. The absolutely unfavorable prognosis that this diagnosis carries with it leads the early consultants in any suspected case to institute delay, hedge an unfavorable diagnosis behind indecision or to attribute the acts indicative of mental aberration to youthful waywardness. The pupillary condition which was noticed by Westphal and more extensively studied by Bumke is present in about three-fourths of the cases of the early stages of the disease but it is an anomaly sometimes seen in perfectly normal minded youths.[1] Its presence also in some cases of manic depressive insanity is not only confusing but is an added indication that we are now including under manic depressive psychosis two quite distinct conditions.

The Westphal-Bumke reaction is not easy to elicit and when observed once should be confirmed by repeated demonstrations. The pupils of the dementia precox patient are almost invariably enlarged but they contract promptly when a bright light is thrown into them. This contraction, however, is not as uniform in the two eyes as it is in health. If now the eye is exposed by raising the upper lid and the observer touches the conjunctiva on the outer side of the globe with the tip of the index finger, there is, in the normal individual, a contraction of the pupil equal to that when a bright light is suddenly thrown into the same eye, but in the dementia precox patient there is no pupillary contraction to touch. This reaction has been much used by a considerable number of psychiatrists, some of whom have made clinical and statistical reports, though the rationale of the reaction still remains a source of mystery.[2]

The very positive indications of the Abderhalden reaction in dementia precox strengthen the pluri-glandular hypothesis of the condition of these unfortunate victims of an unknown toxaemia.[3] Following Fauser's and Wegener's serologic studies in which, very uniformly, the sex glands and one or more of the other glands of internal secretion gave a reaction indicating the presence in the blood of a definite ferment against these organ albumins, the Italian psychiatrists have published a series of careful reports on the histologic morphology of these glands in health and in mental disease. Gorrieri, (Riv. spr. d. Fren., 1913, 39, p. 263) made a careful study of all the organs in the body in a few cases of mental disease of every sort and kind and Todde, (Riv. spr. d. Fren., 1914, 40, p. 233-300) studied the testicle alone in 200 men of whom twenty-five were dead with dementia precox. There were perfectly obvious morphologic defects in the great majority of these glands not to be accounted for by the immediate cause of death, and this was notably the case, not only with the testicle but also with the adrenal, the thyroid and the parathyroid. The studies of Southard on twenty-five brains from dementia precox patients also show obvious physical focal deteriorations in the cerebral hemispheres.

The blood pressure in dementia precox has long been known to be low, but this condition has not aroused much curiosity or research because these patients are so inactive that little else could be predicted. However, Willi Schmidt (M. m. W., 1914, 61, p. 360) early last year published his observations on the inefficiency of the adrenalin to raise the blood pressure in dementia precox. When 0.5 ccm. of the 1-1000 adrenalin solution (Parke, Davis & Co's.) is injected subcutaneously into manic depressive patients or normal individuals, the blood pressure rises forty to eighty millimeters of mercury; but the same injection rarely raises the blood pressure in dementia precox patients at all and sometimes even depresses it.

It is not perfectly clear how this reaction is brought about, but it certainly bears some relation to the Westphal symptom. When a solution of adrenalin is placed in the normal eye it produces no dilation of the pupil. In the eye of a large proportion of dementia precox patients, mydriasis appears, however, and is so prompt and so protracted that its action can not be mistaken. (Cords) Neither as a pressor nor as a mydriatic does adrenalin act in a normal manner in patients with this terrible disease.

In 1849, Thomas Addison connected a destructive condition of the adrenal gland with a wasting disease in which a peculiar bronzing of the skin appeared, (Sydenham Societies Publications). This far off observation led to little research until Brown-Sequard in 1856 experimentally destroyed the adrenals and found that the animals died promptly and that rabbits in particular lived only about nine hours after both adrenals were removed.[4] At the same time Vulpian noticed some color reactions peculiar to the substance of the adrenal glands; a rose red with iodine and a green with ferric chloride.

Not till 1849 was the blood pressure raising or "pressor" action of the gland extract discovered by Oliver and Schafer, (Jour. of Phys., 1894, 17, p. i.) During the following decade the study of this reaction and its biochemistry proceeded with the greatest rapidity in every direction, but all efforts to separate the active principle of the adrenal secretion were unavailing, until in 1901, (1903) J. Takamine isolated a substance which he called "adrenalin" to which T. B. Aldrich assigned the correct empirical formula $C_9 H_{13} O_3N$. In 1904 Dzierzgowski succeeded in synthesizing a substance having the same or similar physiologic action and a German patent for its manufacture was issued.

There are many ways of recognizing adrenalin. The color reactions are very sensitive and recognize high dilutions. Borberg has recently reviewed the colorimetric quantitative methods. (Skand. Arch. of Phys., 1912, 27, p. 341-420). While the ferric sesqui chloride, he finds, recognizes one to a one or even to a three hundred thousand dilution; the persulphate of potassium (or of sodium) test of Pancrazio, (Gas. d. hosp. e. d. clin., 1909, 30, p. 1513) and Ewins (Jour. of Phys., 1910, 40, p. 317-326) detects adrenalin in solution of 1-5,000,000. The method of Folin, Cannon and Denis (Jour. of Biol. Chem., 1913, 13, p. 477-483) is almost as sensitive, if not quite so, and has many other advantages. It detects adrenalin in dilutions of one in 3,000,000, but, unfortunately, it also reacts equally to uric acid in solutions of one-third that dilution, namely one in 1,000,000.

Comessati, (D. m. W., 1909, 35, p. 576) and Fränkel and Allers (Biochem. Z., 1909, 18, p. 40), Zanfrogini (D. m. W., 1909, 35, p. 1752) and Watermann (Arch. f. d. g. Physiol., 1909, 128, p. 48-66) have each proposed tests for adrenalin having some special advantage in the experience of the authors.

The physiologic action of adrenalin is so prompt, so intense and so uniform that the most sensitive methods of recognizing this substance are biologic. Following the almost coincident discovery of the "pressor" action of extract of adrenal gland by Oliver and Schafer (1894) and Szymonowicz (1895) many ingenious and cunning applications of it have been made. Extremely small quantities of adrenalin, 0.000,3 mg. per kilo, are large enough doses to inject intravenously in rabbits and bring about characteristic symptoms. (Cameron, Pro. Roy. Soc. Edin., 1906, 26, p. 157-171). The reaction is very sharp and appears in a few seconds, but it is transient and the blood pressure after a few (at most two to six) minutes falls sharply and then more slowly and after a few minutes there is a secondary wave of action raising the blood pressure very slightly and then disappearing for good. If the blood from such an animal, however, is now injected intravenously into a second animal, there is still enough unconsumed or uninactivated adrenalin to produce the pressor reaction again (Weiss and Harris, Pflügers Arch., 1904, 103, p. 510-514). The rapid return to the normal of the blood pressure so characteristic of the intravenous adrenalin injection is not then due to a chemical reaction between the blood vessels and the base that results in the consumption or the destruction of the adrenalin.

There have been many studies of the "pressor" action of adrenal extracts under various conditions, some of which must be noticed later, but the extract of each of the glands of internal secretion has its own peculiar action. For example, Bürgi and Traczewski, (Biochem. zeit. 1914 66, 417-36) have noticed that with a mixed extract of these glands a stimulating equilibrium was established in the circulation and the heart maintained its normal activity. Each of the several glands of internal secretion has two portions of more or less antagonistic function when measured by any single action. Thus Ossokin (Zent. f. Phys., 1914, 28, p. 59) immunized dogs with extract of the posterior lobe of the pituitary for a sufficient time, after which their sera when injected into other animals produced pronounced and long lasting fall in blood pressure—when the extract of the anterior lobe was used the resulting immunized serum produced a less pronounced and transient pressor action!

In man there is also a rise in blood pressure on the subcutaneous injection of adrenalin, but it is not so sharp or so high as we observe after intravenous injection. When given by the mouth adrenalin is without pressor action but it does cause the contraction of the blood vessels of the mucous surfaces with which it comes in immediate contact. It is on account of this property that it attained its vogue in rhinology. Large doses of adrenalin are toxic and lethal, and even repeated small doses intravenously encourage and are said to promote arterio-sclerosis,[5] but this presumption needs further investigation.

The smooth or involuntary muscles are also acted upon by adrenalin while the striped or voluntary muscles are unaffected. (Yas Kuno, J. of Phys., 1915, 49, p. 139). The muscles of the intestinal tract generally (except the sphincters) are relaxed and under full doses of adrenalin, automatic peristalsis ceases. In most animals on intravenous injection of adrenalin the urinary bladder is relaxed but in some animals it is contracted! The uterus of the rabbit and the pregnant cat contracts, that of the non-pregnant cat relaxes. The isolated uterus of a pregnant cat in a bath of one to 350,000,000 adrenalin solution exhibits tetanic contraction. (Kehrer, Arch. f. exp. Path. u. Phar., 1908, 58, p. 366).

The mydriatic action of adrenalin early noticed by Vincent and described in detail by Lewandowsky was utilized by the Meltzers (Am. J. of Phys., 1904, 11, p. 449-454) as a means of determining the strength of adrenalin solutions. They used for this purpose the isolated eyes of frogs. This test is so delicate that quantities as small as 0.000,000,002 grm. have been detected. Thus the smooth muscles of the isolated eye are paralyzed or relaxed by adrenalin, and also in patients suffering of dementia precox. Karl Basch has recently (D. m. W., 1913, 39, p. 1456) shown that adrenalin reacts upon the pupil of thyroidectomized dogs much less rapidly than upon non-thyroidectomized dogs of the same litter.

The mydriatic action of adrenalin (in experimental animals at least) is heightened or increased by protracted preliminary feeding of extract of the thyroid gland with the idea of immunization. It was also the case even if the pupillary nervous mechanism had been interrupted. This may be interpreted to mean that the blood of these experimental animals contained an antithyroid amboceptor. When a similar experiment was undertaken by feeding other laboratory animals with the extract of the anterior lobe of the pituitary body it produced, after a protracted feeding, a condition of extreme myosis; that is, the pupils of these animals were minutely contracted. There resulted at the same time an exaggerated reaction of the pupils to adrenalin. The feeding of the posterior lobe of the pituitary had no effect on the laboratory animals. (Mattirolo Ganin & DeGamma). This is a condition exactly the antithesis of that observed in dementia precox.

No wholly satisfactory explanation exists of the fact that the uterus of the cat and urinary bladder of many animals react paradoxically to adrenalin. In the uterus of the non-pregnant cat it is presumed that the nature of the myo-neural junctions determines the response of the muscle to adrenalin and to a large number of related amines (Barger & Dale, Jour. of Phys., 1910, 41, p. 19-59) (Elliott, J. of Phys., 1905, 32, p. 401-467 and 1912, vol. 44, p. 374-409). It is possible that the paradox in dementia precox depends in its pupillary phenomenon on the abnormal condition of the myo-neural junctions brought about by the toxins of the primary disease.

There is some reason to think that the toxins, such as we assume are responsible for dementia precox, are capable of changing the character of the myo-neural junctions. These have been furnished by the experiments of Dale (J. of Phys., 1906, 34, p. 163-206) who showed that a preliminary injection of ergotoxin into an animal in which a large rise of blood pressure should be expected was followed by a distinct fall in blood pressure when the "pressor" dose of adrenalin was injected into the vein. Thus the large rise in blood pressure which adrenalin causes in the normal animal is replaced by a smaller depressor effect if ergotoxin has been previously administered.

The dementia precox patient seems in a constant ergotoxin-like intoxication, for the injection of 0.5 ccm. of a 1-1000 adrenalin hydrochloride solution, which is adequate to raise the blood pressure of the normal man and most insane persons 40-80 mm. of mercury, slightly depresses the blood pressure and at the same time fails to produce the normal mydriatic pupillary phenomenon.

This may not, however, be the correct parallel. Further research by the intravenous method of administration of adrenalin is necessary.

Results of experiments on decerebrated cats and rabbits show that adrenalin, epinine-HC_1 and other amines and alkaloids cause constriction of normal bronchioles but that dilation results from these drugs after curare, ergotoxins, apocodeine, pilocarpidine, muscarine, and physostigmine. Tracheal musculature is uniformly relaxed by adrenalin, pilocarpin causes its contraction, and ergomin is without effect. (Golla and Symes, J. of Phar. & Exp. Ther., 1914, 5, p. 87-103.) The subcutaneous and intravenous injection of adrenalin in sufficient doses was shown by Blum (Deut. Arch. f. k. Med., 1901, 71, p. 146) to produce glycosuria, and Straub, (M. m. W., 1909, 56, p. 493) determined the minimum dose that could be safely given without causing glycosuria. This he found to be 0.002 mgm. per minute. Double this rate of injection caused sugar to appear in the urine. The mechanism of adrenalin glycosuria is not yet clear, but those qualified to judge believe that the pancreas is not involved in the process. But, on the other hand, guanin certainly reduces the glucosuric action of adrenalin and the presence of guanin in the pancreas is in some way related to the glycochemic action of this organ. (Degrez & Dorleans, Compt. rend., 1913, 157, p. 946-947.)

It would be interesting to know just how dementia precox patients would compare in glycosuric sensitiveness to adrenalin with the clinical experimental experience of Blum and Straub. This problem lies ready for solution before some young, ambitious clinical psychiatric biochemist. It is well recognized that early in the acute form of dementia precox there is an acetone breath and acetone in the urine, but glycosuria has never been mentioned as a common or conspicuous symptom of this disease.

There are other causes of low blood pressure that must not be overlooked in this connection. The evidences of adrenal disturbances and adrenal incompetency in dementia precox patients are weighty indeed, but there are poisonous amines developed in the intestine that are also depressants of the arterial tension. These poisonous amines are produced from non-poisonous and useful proteins and probably the most likely one affecting dementia precox patients is the beta-iminazolyl-ethylamine which results from the growth of the Bacillus aminophilus intestinalis on a nutrient media containing histidin. This amine is a depressor of arterial tension and a constrictor of the smooth muscle fibres of the bronchi. The liver is the great eliminator of this toxin, but we do not know in exactly what form the excretion appears in the urine—probably it appears as indol-acetic acid. This substance has been found in the urine of one-fifth the healthy and almost one-half of the dementia precox patients in custody. (Ross, Arch. Int. Med., 1913, 12, p. 112.)

The secretion of indol-acetic acid in two cases of dementia precox was greatly affected by the character of the diet, so E. L. Ross, (Arch. Int. Med., 1913, 12, p. 231) concluded that this acid is of endogenous origin. (v, Much, Q. J. M., 1914, 7, p. 439.)

There is one other aspect of the adrenal function which arouses speculation and ought to lead to still more optimistic research in dementia precox. The relation between hydrocephalus and other diseases of the brain and the adrenals was first noticed by Wagler (Blumenbach's med. Bibliothek., 1788, 3, p. 629) in 1788, and afterwards by many authors, especially by Lomer (Vir. Arch., 1883, 98, p. 366). Anencephale are devoid of adrenal bodies. The destruction of the adrenals brings on morbid cerebral changes. Southard (Am. J. Insanity, 1914-15, 71, p. 383-403 and 603-671,) has found hydrocephalic conditions in nineteen out of twenty-five dementia precox patients lately studied. Almost fifteen years ago Czerny (Cent. f. alg., Path. u. path. Anat., 1899, 10, p. 281-286) related hydrocephalus to the adrenals by injecting the cerebrospinal lake of animals with finely divided coloring matter and later finding the adrenal medula stained with the coloring matter and connected with the cerebrospinal lake by a special series of highly stained lymph canals. He also found the medulla of the adrenals in hyprocephalus deficient and sclerotic, (Levy, J., Thesis, Berlin, 1913.)

Can it be possible that some peripheral infection so acts upon the pluriglandular system in cases of dementia precox as to destroy, pervert or misdirect the adrenal and bring about those serious cerebral disturbances that give color to the disease we know as dementia precox? An analogy is to be found in Grave's disease, or exophthalmic goiter, which is often the result of tonsillar and faucial infection.

It is not unreasonable to expect some method of clinically determining the adrenalin content of the blood. O'Connor (M. m. W., 1911, 58, p. 1439, and Arch. exp. Path. u. Phar., 1912, 67, p. 195-232) and Stewart (J. exp. Med., 1912, 15, p. 547-569) agree that up to the present time this desirable end has not been attained. There may still be means of determining the adequacy of the various glands in early and subsequent stages of dementia precox.

In a few instances decompression operations in cases believed to be cases of dementia precox have been followed by an arrest of the disease.[6] The fact that the blood vessels within the viscera, especially within the brain, are affected by adrenalin in a depressing and paralyzing manner, (Cow., J. of Phys., 1911, 42, p. 125-143) while other blood vessels are contracted, may bear some relation to the hydrocephalus and the mental symptoms. The cranial capacity in dementia precox patients is limited as compared with the brain weight. The index of Tigges' and the ratio between the brain weight and the cranial capacity is increased in dementia precox.

I cannot conclude this incomplete and hasty review of the evidence that the adrenal gland is under strong suspicion of having a leading part in the production of that symptom complex we call dementia precox, without referring to the influence of adrenalin on the salivary secretion. In some stage of nearly every case of dementia precox salivation is a conspicuous symptom. Now Langely claims (J. of Phys., 1901, 27, p. 237-256) that the injection of adrenalin increases salivary secretion.

Equally significant to the clinical observer is the fact that asphyxia increases the secretion of adrenalin. (Cannon & Hoskins, Am. J. of Phys., 1911, 29, p. 274-279.) Asphyxia is a very common and long continued symptom of dementia precox, and it seems, in some cases at least, to be due to the spasm and tetanic contraction of the muscles of respiration. Sulphhemoglobinaemia is occasionally seen in the course of catatonia. In spite of everything the blood pressure in dementia precox is low, (Cazzamili, Riv. spr. fren., 1913, 39, p. 98) and the injection of adrenalin will not raise it.

The amount of adrenalin in the adrenals is diminished in asphyxiation. The diminution in the amount of adrenalin is often regarded as the cause of death. In fact the lowering of the adrenal content is a result of the asphyxiation of the organism. (Czubalski, Zent. f. Physio., 1914, 27, p. 580.)

CONCLUSIONS

1. Adrenalin is the only chemically established organ secretion and furnishes an ideal base for physiologic study.
2. The action of adrenalin on patients with the clinical diagnosis dementia precox differs from its action on healthy persons and resembles its action on animals poisoned with ergotoxin.
3. The insensibility of dementia precox patients to the "pressor" action of adrenalin and its abnormal mydriatic action furnish a helpful means of diagnosis which promise with the coincident application of the defensive ferment reaction, both suggestive therapeutic possibilities and avenues of hopeful research.

---

[1] Bumke, Oswald: Pupillen-störungen hei Geistes-und Nervenkrankheiten. Jena, 1911, esp. pp. 249-268.

[2] The increased intracranial pressure which the dilated pupil might reasonahly portend has been assumed to he the cause of death in two cases of catatonia recently

studied by Nissl, (his last Beitrage published April 11, 1914.) He found "brain swelling" or "wet brain." As usual in dementia precox the brain was too heavy for the cranial capacity in both Nissl's cases. See also in this connection Klebelsberg, "Ueber plötzliche Todesfälle bei Geisteskrankheiten." Z. f. d. g. Neur. u. Ps., 1914, Orig. 25, p. 253 and Leppmann, "Ein Fall von Heilung einer Psychose durch Kopfverletzung." Jahrb. d. schles. Gesellsch. f. vaterl. Kult., 1884, 62, p. 157.

3. A complete review of the literature of the application of the Abderhalden reaction in psychiatry was made by Johann Fischer. D. m. W., 1913, 39, p. 2138 and more recently by Nieszytka, D. m. W., 1914, 40, p. 1519. Z. f. d. g., Neur. u. Ps. 1914, Vol. 26, p. 546-563.

4. The experiments of Brown-Sequard have lately been repeated by Elliot (Jour. of Phy., 1914, 49, p. 38-53) upon a large scale with twenty-five cats. The second gland was usually removed from three weeks up to nine months after the first. No one of the twenty-five cats died of the first operation and only one cat recovered completely after the removal of the second gland. It was examined and killed nine weeks after the second operation. Nine of the twenty-five cats died on the second or third day. The second gland that was removed was obviously hypertrophied. Sixteen of the cats lived for six or ten days and one of these died on the twenty-second and one on the twenty-third day and one was killed in the ninth week. Most of the cats that lived six days or more had two or three acute ulcers of the stomach, a token of the full digestive powers of the gastric juice. This seems remarkable when we remember that ulcer of the stomach is not seen in patients with Addison's disease, (Finzi, Vir. Arch., 1913, 214, p. 413-432, Biblio.)

Elliot notices that the approach of death was announced by the development of a characteristic weakness. When placed upon the floor the cat would walk a few steps and then stand switching its tail, bothered by the difficulty of walking.

Despite this characteristic prostration the animal could be aroused by an alarm to fully coordinated and fairly strong muscular movements. There was no paralysis of the skeletal muscles or their nerves. This was very evident when the moribund cat was placed under a large bell jar and smelt the ether intended for its anesthetic. The cat moved almost as freely and as quickly as a normal animal would have done and there was also the usual free salivation. The blood pressure of the dying animal was very low, ten to fifteen millimeters, and was raised very little by its struggles. The blood supply of the cerebral hemispheres became scant and a stiffness set in the fore limbs while the hind limbs commenced an automatic walking rhythm. The intravenous injection of a small amount of adrenalin restored the blood pressure with the full circulation, the rigidity disappeared.

5. Since the use of adrenalin in asthma, this observation has been contradicted by the clinical experience of many reliable observers. (Van Leersum & Rassers, Beitrag zur Kenntnis des experimentellen Adrenalin-Atherons. Z. f. exp. Path., 1914, 16, p. 230.)